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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,488	01/15/2004	David G. Gorenstein	UTMB:1019RCE	5963

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,488	GORENSTEIN ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-12,14-17 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-12,14-17 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/22/07 & 9/18/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/425,798, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The parent application does not provide support for thioaptamers that mediate gene silencing, including thioaptamers that are siRNAs that mediate gene silencing through a RISC complex, thus the priority date for siRNA thioaptamers as recited in claims 7 and 10-12 and claim 1 to the extent that it embraces the embodiments of claims 7 and 10-12 is January 15,

2004, the filing date of the instant application. If applicant believes that any of the prior applications provide support for this embodiment, it should be pointed out with particularity in the response to this action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Baracchini (US 5,801,154, of record).

The claimed invention is directed to isolated thioaptamers 15-25 nucleotides in length that mediate gene silencing and comprise one or more ribonucleotide monophosphates, which is the equivalent of a phosphorothioate linkage. Thioaptamer is defined in the specification on page 6 as encompassing antisense oligonucleotides and ribozymes. The thioaptamer may comprise a 3' OH group and may be composed of ribonucleotides or deoxyribonucleotides. The thioaptamer may be fully or imperfectly complementary to the target gene and the silencing can occur through repression of translation, mRNA cleavage or binding to a 3'UTR. The thioaptamers can comprise compositions with a carrier.

Baracchini et al. disclose antisense oligonucleotides that are targeted to and inhibit multi-drug resistance associated protein. These antisense oligonucleotides are 8-30 nucleotides in length, contain phosphorothioate linkages, are comprised of RNA or

DNA, are targeted to numerous regions including the 3'UTR and are provided as compositions comprising a carrier (see claims 1 and 4-6 and columns 6-7). At column 3, lines 32-34 Baracchini et al. disclose that antisense oligonucleotides do not have to be 100% complementary to the target gene. It is known in the art that antisense inhibition occurs through an RNase H mechanism that cleaves mRNA and prevents translation of the mRNA into protein.

Thus, Baracchini et al. disclose all limitations of and anticipate claims 1-4, 6, 8, 9, 15-17 and 37.

Claims 1-4, 6, 7, 9 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550).

The claimed invention is directed to isolated thioaptamers 15-25 nucleotides in length that mediate gene silencing and comprise one or more ribonucleotide monophosphates, which is the equivalent of a phosphorothioate linkage. In specific embodiments the thioaptamer comprises a 3' OH group and may be composed of ribonucleotides or deoxyribonucleotides. The thioaptamer can silence a gene can occur through mRNA cleavage.

Agrawal et al. disclose self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. On pages 15-16 Agrawal et al. disclose the oligonucleotide is a single nucleic acid strand that forms a double stranded structure and the self-complementary region of the oligonucleotide is fully complementary to the hybridizing region to form a duplex. On page 8 Agrawal et al. disclose that the self-stabilized oligonucleotides are composed of ribonucleotides,

deoxynucleotides and/or modified nucleotides. At page 14 Agrawal et al. disclose that the oligonucleotide can comprises phosphorothioate linkages. On pages 17, line 27 through page 18 Agrawal et al. disclose that the self-stabilized oligonucleotides can be administered to the cells of an animal to inhibit gene expression in the animals, which requires formulation with a pharmaceutically acceptable carrier.

Thus, Agrawal et al. disclose all limitations of and anticipate claims 1-4, 6, 7, 9, 14-16 and 37.

Claims 1, 7, 10-12 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Parrish et al. (Molecular Cell 2000, of record).

The claimed invention is directed to thioaptamers that mediate gene silencing. In specific embodiments the thioaptamer comprises a double stranded RNA fully complementary to a target that silences the gene by mRNA cleavage, is part of a RISC complex, is produced by a DICER complex or is a siRNA.

Parrish et al. disclose double stranded RNAs comprising phosphorothioate linkages that are complementary to and inhibit the *unc-22* gene of *C. elegans* by RNA interference. The addition of these RNAs to *C. elegans* requires formulation with a pharmaceutically acceptable carrier. As evidenced by the post-filing art of Zhang et al. (of record), Dicer is a multidomain ribonuclease that processes long dsRNAs to fragments of 21-25 nucleotides having 3'-OH termini during RNA interference and is part of the RISC complex. Although Parrish et al. are silent as to the cleavage of long dsRNAs into double stranded duplexes 15-25 nucleotides in length having 3'-OH termini, the long dsRNA molecules disclosed by Parrish et al. are necessarily cleaved

into such duplexes. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. The claiming of an unknown property which is inherently present in the prior art does not necessarily make the claim patentable. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. Inherent anticipation does not require recognition in the prior art. Since Parrish et al. teach phosphorothioate dsRNA and the resultant RNA interference, and it has since been discovered that this effect is mediated by the activity of Dicer, which cleaves long dsRNA into fragments that are 15-25 nucleotides long, the teachings of Parrish et al. anticipate the instant invention.

Thus, Parrish et al. disclose all limitations of and anticipate claims 1, 7 and 10-12.

Response to Arguments

Applicants traverse the rejection over Baracchini et al. by arguing this reference does not disclose every element of the claims, specifically that Baracchini teaches that modifications may include phosphorothioates but makes no indication that the modification may include a partially modified backbone. Applicants further note that in the working examples, the oligonucleotides are either all phosphorothioate or all phosphodiester. Applicants conclude that the claims as amended are not anticipated by Baracchini and assert that Baracchini is non-enabling and does not disclose and enable each and every limitation to the present invention.

Applicants' arguments are not persuasive because Baracchini et al. do more than contemplate oligonucleotides with partial phosphorothioate backbones; table 4 discloses oligonucleotides having a partially modified phosphorothioate backbone. Additionally, claim 6 specifically recites the limitation that the oligonucleotides of claim 1 comprise one or more phosphorothioate linkages. This claim embraces oligonucleotides having from one to all linkages as phosphorothioate. The argument with regard to enablement of Baracchini et al. is not persuasive because no specific arguments are presented why the reference is not enabled.

Applicants traverse the rejection over Agrawal et al. by arguing that the reference does not disclose the thioaptamer may have a partially thiomodified phosphodiester backbone and further assert the term phosphorothioate linkage is not interchangeable with the term monophosphate asserting that clearly there are substantial differences between the two that do not allow interchangeable or as equivalent use.

This argument is not persuasive because Agrawal et al. clearly state that the oligonucleotides of his invention can comprise phosphorothioate linkages, providing a generic disclosure of oligonucleotides having from one to all internucleotide linkages substituted with a phosphorothioate. Applicants assert there are substantial differences between the term monophosphate and phosphorothioate and the terms are clearly not equivalent or interchangeable but provide no specific arguments of the differences that would lead one to conclude they are not equivalent. Indeed applicants' amendment describes the instant invention as oligonucleotides having monophosphorothioate or

phosphorodithioate modifications. Page 5 of the most recent amendment refers to the specification and states:

> "...the application (paragraphs [0030-0031]) defines the term thioaptamer as oligonucleotides (ODNs) in which one or more of the four constituent nucleotide bases of an oligonucleotide are analogues of nucleotides that normally form the DNA or RNA backbones. The analogues include thiophosphates having sulphur in place of one or more of the non bridging oxygens bound to the phosphorus. For example, monothiophosphates (αS) have only one sulfur and are thus chiral around the phosphorus center; while dithiophosphates (αS2) are substituted at both oxygens and are thus achiral. The modified nucleotide thioaptamer include one or more monophosphorothioate (e.g., dATP(αS), dTTP(αS), dCTP(αS), dGTP(αS), rUTP (αS) rATP(αS), rCTP(αS) or rGTP(αS)) or phosphordithioate (e.g., dATP(αS2), dTTP(αS2), dCTP(αS2), dGTP(αS2), rATP(αS2), rCTP(αS2), rGTP(αS2) or rUTP(αS2)) linkages incorporation by polymerases."

Applicants further argue that oligonucleotides of Agrawal are merely self complementary and do not hybridize to a separate nucleic acid sequence. This is not persuasive because the oligonucleotides of Agrawal et al. are specifically described as comprising a target hybridizing region, a sequence that hybridizes to a separate nucleic acid target sequence.

Applicants additionally argue that Agrawal is non-enabling and does not disclose and enable each and every limitation to the present invention

The argument with regard to enablement of the reference is not persuasive because no specific arguments are presented why the reference is not enabled.

Applicants traverse the rejection over Parrish et al. by arguing the reference does not teach all elements of the invention, specifically that Parrish does not disclose a thioaptamer where all of the non-adjacent dA, dC, dG, or dT phosphate sites of the modified nucleotide aptamer are replaced with phosphorothioate groups, all of the non-adjacent dA, dC, dG, and dT phosphate sites of the modified nucleotide aptamer are

replaced with phosphorothioate groups; or substantially all non-adjacent phosphate sites of the modified nucleotide aptamer are replaced with phosphorothioate groups.

These arguments regarding whether Parrish discloses replacement of non-adjacent nucleotides with phosphorothioate groups are not persuasive because the claims do not require that the substitution be at non-adjacent nucleotides.

Applicants further allege that Parrish does not disclose oligonucleotides wherein no more than three adjacent phosphate sites of the modified nucleotide aptamer are replaced with phosphorodithioate groups or that the thioaptamers may be obtained by adding bases enzymatically using a mix of four nucleotides, wherein one or more of the nucleotides are a mix of unmodified and thiophosphate-modified nucleotides.

The argument with regard to replacing no more than three adjacent phosphates is not persuasive because this limitation is not required by the instant claims. As for replacement of more than one nucleotides with thiophosphates, this is not persuasive because Parrish discloses at page 1081, second column RNAs produced by modification of two bases are modified.

Applicants additionally argue that Parrish is non-enabling and does not disclose and enable each and every limitation to the present invention.

The argument with regard to enablement of the reference is not persuasive because no specific arguments are presented why the reference is not enabled

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent

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/Tracy Vivlemore/
Examiner
Art Unit 1635

TV
March 17, 2008